REMARKS

Claims 4, 5, 8, 15, and 30-44 are pending, and were rejected by the Examiner. In light the following remarks, Applicants respectfully request reconsideration and allowance of claims 4, 5, 8, 15, and 30-44.

Rejections under 35 U.S.C. § 112

Applicants acknowledge the Examiner's withdrawal of the rejections under 35 U.S.C. § 112, second paragraph and 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 103

The Examiner maintained the rejection of claims 4, 5, 8, 15, and 30-40 under 35 U.S.C. § 103(a) as being unpatentable over Donovan (1998 *Leukemia* 12:593-600) and Carter (1990 *Br. J. Haematol.* 74:424-431). The Examiner stated that "Donovan *et al.* teach that IL-1β can differentiate between the diagnosis of MM, MGUS, and an unrelated condition..." The Examiner also stated that "one of ordinary skill in the art at the time of the invention would have known from the teaching of Donovan that evaluating the status of individuals with MGUS or pre-MM conditions such as SMM could have their status monitored or compared to controls because the level of IL-1β goes from undetectable to detectable. One of ordinary skill in the art would know that IL-1 is secreted so a cell free supernatant of the MC can be assayed for the presence of IL-1 as well."

Applicants respectfully disagree, and submit that a review of the art as a whole indicates the uncertainty as to whether the presently claimed methods would be useful for predicting the likelihood of progression to MM. First, the Donovan *et al.* reference does not provide as much certainty as the Examiner implies. For example, Tables 1, 2, and 3 of the Donovan *et al.* reference show that IL-6 mRNA was detected in sorted bone marrow cells only from MM patients, and then only in less than half (5 of 11) of the MM samples examined. All five of the cell samples in which IL-6 mRNA was detected had a high plasma cell labeling index, indicative of an elevated proliferation rate. However, three other samples with a high labeling index did not display detectable IL-6 mRNA levels. Thus, IL-6 mRNA was detected in only a fraction of the MM samples examined by the authors of the Donovan *et al.* reference. Furthermore, the

small number of patient samples examined by Donovan *et al.* does not provide statistically relevant results.

Furthermore, the second paragraph on page 599 of the Donovan *et al.* reference states that sorted plasma cells from only one MGUS patient were found to express IL-1β mRNA. This paragraph further states that "[f]ollow-up of IL-1β-positive MGUS patients . . . may determine whether aberrant expression of IL-1β is predictive of progression to active MM" (emphasis added). Thus, the Donovan *et al.* reference merely provides an invitation to experiment, but does not provide any reasonable expectation of success for using the presently claimed methods.

Second, the Carter *et al.* reference does not remedy the deficiency of the Donovan *et al.* reference. The Carter *et al.* reference reports a method for co-culturing myeloma cells with bone marrow stromal cells and then determining IL-6 activity in culture supernatants. The Carter *et al.* reference fails to report using this method, or any other method, to measure IL-6 in samples from subjects with MMRPD such as MGUS or SMM. In addition, the teachings of the Carter *et al.* reference are contradicted by other references. The Carter *et al.* reference discloses that anti-IL-1β antibodies partially inhibited IL-6 secretion from marrow stromal cells cultured with myeloma cells. See, Table III and the last full paragraph on page 428 of the Carter *et al.* reference. In contrast, the Thomas *et al.* reference [(1998) *Leuk. Lymphoma* 32:107-119; copy enclosed] reports that anti-IL-1β antibodies did not block IL-6 production by bone marrow fibroblasts cultured with myeloma cells. See, page 113 of the Thomas *et al.* reference. Thus, the relationship between IL-1 and IL-6 was unclear at the time Applicants filed.

Other references in the art also indicate the uncertainty as to whether IL-6 protein levels indicate the likelihood of progression of MMRPD. For example, the Choi *et al.* reference [(2000) *Blood* 96:671-675; copy enclosed] states that IL-6 and IL-1β were undetectable in samples from patients with stage III MM, that *in vivo* studies have failed to confirm a role for either IL-1β or IL-6 in the pathogenesis of myeloma bone disease, and that factors other than these cytokines are implicated in the pathogenesis of the disease. *See,* the first and second full paragraphs on page 674. In addition, the Kiss *et al.* reference [(1994) *Leuk. Lymph.* 14:335-340; ref. AR on the IDS submitted September 17, 2002] reports that no correlation was observed between IL-6 levels and disease status in patients with MM, plasmacytoma, or benign monoclonal gammopathy. *See,* e.g., the left column on page 338 and the final paragraph on page

339. Thus, the relationship between IL-6 and myeloma or MMRPD was unclear at the time Applicants filed.

Third, the Examiner concludes that one of ordinary skill would have known from the teachings of the Donovan *et al.* reference that "the level of IL-1β goes from undetectable to detectable" in individuals having pre-MM conditions. However, it is a quantitative change rather than a qualitative change that is required to differentiate the SMM group. In general, MGUS and MM may be differentiated on clinical grounds. However, patients with SMM that will remain stable versus those that will progress to active MM cannot be distinguished using current clinical or research criteria. Moreover, Table I of the Donovan *et al.* reference shows that IL-1β mRNA was detected in a sample from a patient with SMM. This result indicates that merely detecting IL-1β mRNA is not sufficient to determine whether a patient with SMM will progress to MM. Thus, the inventors developed a quantitative protein assay that differentiates patients with stable SMM from those with progressive SMM.

There was uncertainty in the art as to when and whether IL-1β protein is produced in myeloma cells, since it was known that IL-1β message may not be translated into IL-1β protein. The uncertainty regarding the correlation between IL-1β mRNA and protein synthesis is detailed in, for example, the Dinarello reference [(1996) *Blood* 87:2095-2147; ref. AL on the IDS submitted September 5, 2001] and the Schindler *et al.* reference [(1990) *J. Biol. Chem.* 265:10232-10237; copy enclosed]. In particular, the Dinarello reference discloses that primary IL-1β transcripts do not always yield mature mRNA. *See*, the left column on page 2099. The Dinarello reference also discloses that after translation, proIL-1β remains cytosolic until it is cleaved and transported out of the cell. This reference further teaches that not all cells process proIL-1β and secrete mature IL-1β. *See*, page 2100. In addition, the Schindler *et al.* reference teaches that in human peripheral blood mononuclear cells (PBMC), IL-1β protein synthesis is regulated at both the transcriptional and the post-transcriptional or translational levels. In particular, the Schindler *et al.* reference teaches that IL-1β mRNA was detected in PBMC after incubation with lipopolysaccharide, but IL-1β protein was not detected. *See*, the first paragraph of the Results section on page 10233.

Furthermore, the Sati *et al.* reference [(1999) *Br. J. Haematol.* 104:350-357; ref. AT on the IDS submitted September 17, 2002] indicates that while IL-1β message was detectable in clonal plasma cells in bone marrow samples from patients with MM and MGUS, IL-1β protein was not detectable in these cells. *See*, the first two paragraphs of the Results section on page 352. This reference further suggests that myeloma cells *in vivo* are unable to produce IL-1β. *See*, the penultimate sentence of the Abstract. Thus, the art provided no certainty that IL-1β protein would be present in myeloma cells to stimulate IL-6 production.

At least four other reports have indicated that IL-1β protein is not detectable using standard ELISA assays. See, for example, the final paragraph of the Results section on page 449 of the Borset *et al.* reference [(1993) *Br. J. Haematol.* 85:446-451; ref. AQ on the IDS submitted September 17, 2002]; the first full paragraph on page 674 of the Choi *et al.* reference (*supra*); the final paragraph on page 338 of the Kiss *et al.* reference (*supra*); the final paragraph of the Results section on page 1109 of the Chauhan *et al.* reference [(1996) *Blood* 87:1104-1112; copy enclosed]. Finally, the Thomas *et al.* reference (*supra*) reports that antibodies against IL-1β did not interfere with IL-6 production by stromal cells co-cultured with myeloma cells. *See*, the paragraph spanning pages 112 and 113.

In view of these teachings, a person of skill in the art would not have had a reasonable expectation of success for using the presently claimed methods to evaluate the likelihood of progression to MM. Thus, the combined teachings of the Carter *et al.* and Donovan *et al.* references do not render the presently claimed methods obvious.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 4, 5, 8, 15, and 30-40 under 35 U.S.C. § 103(a).

CONCLUSION

Applicants respectfully submit that claims 4, 5, 8, 15, and 30-44 are in condition for allowance, which action is requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: September 14, 2004

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